CHAPTER 10

10 Pharmacology and clinical uses of testosterone

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10.1 Historical development of testosterone therapy

The first experimental proof that the testes produce a substance responsible for virility was provided by Berthold (1849). He transplanted testes from roosters into the abdomen of capons and recognized that the animals with the transplanted testes behaved like normal roosters: "They crowed quite considerably, often fought among themselves and with other young roosters and showed a normal inclination to hens". Berthold concluded that the virilizing effects were exerted by testicular secretions reaching the target organs via the bloodstream. Berthold's investigation is generally considered the origin of experimental endocrinology (Simmer and Simmer 1961). Following his observation various attempts were made to use testicular preparations for therapeutic purposes. The best known experiments are those by Brown-Séquard (1889), who tried testis extracts on himself (which can at best have had placebo effects). The first testicular extracts with demonstrable biological activity were prepared by Loewe and Voss (1930) using the seminal vesicle as a test organ. Finally, the groundstone for modern androgen therapy was laid when steroidal androgens were first isolated from urine by Butenandt (1931), testosterone was obtained in crystalline form from bull testes by David et al. (1935) and testosterone was chemically synthesized by Butenandt and Hanisch (1935) and Ruzicka and Wettstein (1935).

Immediately after its chemical isolation and synthesis testosterone was introduced into clinical medicine (unthinkable if it had happened today) and used for the treatment of hypogonadism. Since testosterone was ineffective orally it was either compressed into pellets and applied subcutaneously (see Chapter 12 by Handelsman, this volume) or was used as 17α-methyltestosterone. In the 1950s longer acting injectable testosterone esters (Junkmann et al. 1957) became the preferred therapeutic modality. In the 1950s and 1960s chemists and pharmacologists concentrated on the chemical modification of androgens in order to emphasize their erythropoietic or anabolic effects (Kopera 1985). These preparations never played an important role in the treatment of hypogonadism. In the late 1970s the orally effective testosterone undecanoate was added to the spectrum of testosterone preparations clinically used (Coert et al. 1975; Nieschlag et al. 1975). Finally, transdermal testosterone applied either through scrotal skin (Bals-Pratsch et al. 1986) or non-scrotal skin (Mazer et al. 1992) was introduced into clinical practice in 1994 and 1995 respectively, first in the USA and later also in other countries.

10.2 General considerations

Although testosterone has been in clinical use for over 60 years, it has never received much interest from clinical research. This is partly due to the fact that hypogondal men requiring testosterone treatment constitute only a small minority of all patients and hypogonadism is not a life-threatening disease. Since development of new preparations is mainly a task of the pharmaceutical industry and hypogonadal patients did not promise to contribute a substantial economic profit, development of testosterone preparations was slow. Only recently has the question of testosterone treatment of senescent men and, to a certain extent also the search for a hormonal male contraceptive spurred interest in the pharmacology and application of testosterone

Today oral, injectable and transdermal testosterone preparations are available for clinical use. There are practically no studies available comparing the various preparations with the goal of identifying the optimal preparation for substitution purposes. While the older injectable preparations, which are still the predominant form for substitution, produce supraphysiological serum testosterone levels, the newer preparations achieve levels in the physiological range. We are only beginning to understand which serum levels are required to achieve the various biological effects of testosterone and to avoid untoward side-effects. In particular, very little is known about long-term effects of testosterone therapy caused by different preparations. Under these circumstances it appears that the consensus reached by a Workshop Conference on Androgen Therapy organised jointly by WHO, NIH and FDA in 1990 still provides the best therapeutic guidelines: "The consensus view was that the major goal of therapy is to replace testosterone levels at as close to physiologic concentrations as is possible" (WHO 1992). Until other evidence is provided, all testosterone preparations will best be judged by this principle.

Another important question is which androgen preparation should be used for clinical purposes. Numerous androgenic steroids have been synthesized and used clinically in the past. The synthetic androgens were produced with the aim to enhance selectively certain aspects of testosterone activity e.g. the anabolic effect on muscles or the hematopoietic effect. Some of these molecules proved to have toxic side-effects in particular upon long-term use (as required for substitution of hypogonadism) or the desired effects were never proven in controlled clinical trials (as advocated by evidence-based medicine). In addition, some of these steroids could not be converted to 5α-DHT or estrogen as is testosterone and therefore cannot develop the full spectrum of acitivities of testosterone. The important biological significance

of these conversions is described in Chapter 1 (by Rommerts) and 2 (by Quigley) of this volume. For these reasons, the synthetic preparations have almost disappeared from the market and testosterone as produced naturally is the prevailing androgen used in clinical medicine. In its various preparations testosterone has been on the market for over 6 decades and as one of the oldest "drugs" in clinical use has demonstrated its high safety. However, new insights into the molecular mechanisms of androgen action may lead to the development of steroids suited for specific purposes. As an example, 7α-methyl-19-nortestosterone may be quoted, as it is experiencing a renaissance due to its high androgenicity combined with low prostatotropic effects shown in animal experiments (Kumar et al. 1997; Suvisaari et al. 1997). Whether such steroids may become useful and safe for clinical use remains to be seen.

This chapter provides an overview of the various conventional and new testosterone preparations and discusses the clinical use of testosterone. Some aspects will be expanded in the following chapters.

10.3 Pharmacology of testosterone preparations

As all other androgens, testosterone derives from the basic structure of androstane. This molecule consists of three cyclohexane and one cyclopentane ring (perhydrocyclopentanephenanthrene ring) and a methyl group each in position 10 and 13. Androstane itself is biologically inactive and obtains activity through oxygroups in position 3 and 17. Testosterone, the quantitatively most important androgen synthesized in the organism, is characterized by an oxo group in position 3, a hydroxy group in position 17 and a double bond in position 4 (Fig. 10.1).

To make testosterone therapeutically effective three approaches have been used:

1) different routes of administration,
2) esterification in position 17, and
3) chemical modification of the molecule.

In addition, these approaches have been combined. Since of practical clinical relevance, the route of administration is used here for categorizing the various testosterone preparations (overview in Table 10.1).

10.3.1 Oral administration

10.3.1.1 Free testosterone

Free unesterified testosterone as physiologically secreted by the testes would appear to be the first choice when considering substitution therapy. When ingested orally in the free form testosterone is absorbed well from the gut but is effectively metabolized and inactivated in the liver before it reaches

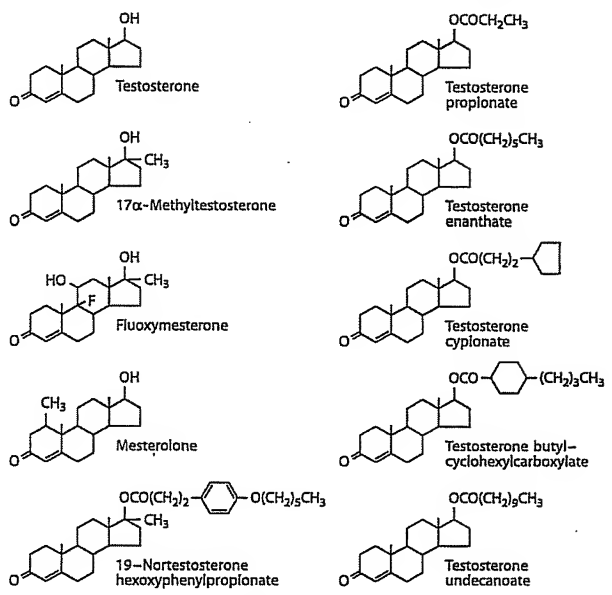

Fig. 10.1. Molecular structure of testosterone and clinically used testosterone esters and derivatives

the target organs ("first-pass-effect"). Only when a dose of 200 mg is ingested, which exceeds 30 fold the amount of testosterone produced daily by a normal man, the metabolizing capacity of the liver is overruled. With such doses an increase in peripheral testosterone blood levels becomes measurable and clinical effects can be observed (Daggett et al. 1978; Johnsen et al. 1974; Nieschlag et al. 1975, 1977). The testosterone-metabolizing capacity of the liver, however, is age- and sex-dependant. An oral dose of 60 mg free testosterone does not affect peripheral testosterone levels in normal adult men, but produces a significant rise in prepubertal boys and women (Nieschlag et al. 1977). This demonstrates that testosterone induces liver enzymes responsible for its own metabolism (Johnsen et al. 1976). When the liver is severely damaged its metabolizing capacity decreases. Thus, in patients with liver cirrhosis a dose of 60 mg testosterone (ineffective in normal men) produces high serum levels (Nieschlag et al. 1977).

Since hypogonadal men usually have normal liver function 400–600 mg testosterone must be administered daily if the patient is to be substituted by oral testosterone (Johnsen 1978; Johnsen et al. 1974). Besides the fact that such high steroid concentrations are uneconomical, the possibility of toxic side-effects of such huge testosterone doses cannot be excluded, especially when given over long periods of time as required for substitution therapy.

Table 10.1. Mode of application and dosage of various testosterone preparations

Preparation	Route of application	Full substitution dose
In clinical use		
Testosterone enanthate	Intramuscular injection	200–250 mg every 2-3 weeks
Testosterone cyplonate	Intramuscular injection	200 mg every 2 weeks
Testosterone undecanoate	Oral	2–4 capsules à 40 mg per day
Transdermal testosterone patch	Scrotal skin	1 membrane per day
Transdermal testosterone patch	Non-scrotal skin	1 or 2 systems per day
Testosterone implants	Implantation under the abdominal skin	3–6 implants à 200 mg every 6 months
Under development		
Testosterone cyclodextrin	Sublingual	2,5–5,0 mg twice daily
Testosterone undecanoate	Intramuscular injection	1000 mg every 8–10 weeks
Testosterone buciclate	Intramuscular injection	1000 mg every 12–16 weeks
Testosterone microspheres	Intramuscular injection	315 mg for 11 weeks
Obsolete		
17α-Methyltestosterone	Oral	(25–50 mg per day)
Fluoxymesterone	Sublingual	(10–25 mg per day)
	Oral	(10–20 mg per day)

However, in a small group of patients treated for as long as seven years with oral testosterone such side-effects have not been observed (Johnson 1978). Nevertheless, oral administration of free testosterone has not become a generally accepted method for therapeutic purposes.

As a relict of experiments performed last century (see 10.1), preparations containing animal testis extracts or dried organ powder are still being manufactured and are available on the market. Although synthesized in the testis, the testosterone content of these preparations is fairly low since the testis, in contrast to other endocrine glands (such as the thyroid), does not store its hormonal products. Moreover, the testosterone in these orally consumed products cannot become effective for the reasons described above. Such preparations may at best exert placebo effects and do not belong to a rational therapeutic repertoire.

10.3.1.2 17α-Methyltestosterone

Several attempts have been made to modify the testosterone molecule by chemical means in order to render it orally effective, i.e. to delay metabolism in the liver. In this regard, the longest known testosterone derivative is 17α-methyltestosterone (Ruzicka et al. 1935) which is a fully effective oral androgen preparation. 17α-methyltestosterone is quickly absorbed and maximal blood levels are observed 90 to 120 minutes after ingestion. The half-life in blood amounts to approximately 150 minutes (Alkalay et al. 1973).

Ever since this steroid was introduced for clinical use, repeated reports about toxic side-effects such as an increase in serum liver enzymes (Carbone et al. 1959), cholestasis of the liver (de Lorimer et al. 1965; Werner et al. 1950), and peliosis of the liver (Westaby et al. 1977) have appeared. It is of interest that humans are more susceptible to the hepatotoxic effects of methyltestosterone than rats (Heywood et al. 1977a) or dogs (Heywood et al. 1977b). Later on, an association between long-term methyltestosterone treatment and liver tumors was found (Farrell et al. 1975; Goodman and Laden 1977; Boyd and Mark 1977; Paradinas et al. 1977; Coombes et al. 1978; Falk et al. 1979; Bird et al. 1979; McCaughan et al. 1985). While these side-effects appear to be clearly related to methyltestosterone application, the isolated observation of a seminoma in a 36-year old man on high-dose methyltestosterone seems rather incidental (Vogelzang et al. 1986).

The side-effects are due to the alkyl group in the 17α-position and have also been reported for other steroids with this configuration (Krüskemper and Noell 1967). Because of the side-effects methyltestosterone should no longer be used therapeutically, in particular since effective alternatives are available (Nieschlag 1981). The German Endocrine Society declared methyltestosterone obsolete in 1981 and the German Federal Health Authority ruled that methyltestosterone should be withdrawn from the market (Methyltestosterone 1988). In other countries, however, methyltestosterone is still in use, a practice which should be terminated.

10.3.1.3 Fluoxymesterone

The androgenic activity of fluoxymesterone was enhanced over that of testosterone by the introduction of fluorine and the addition of a hydroxy group into the steroid skeleton of testosterone. This substance also contains a 17α-methyl group and accordingly there is a risk of hepatotoxicity with long-term use. Therefore, this androgen has disappeared from the market.

10.3.1.4 Mesterolone

Mesterolone can be considered a derivative of the 5α-reduced testosterone metabolite 5α-dihydrotestosterone (DHT) which is protected from fast metabolism in the liver by a methyl group in position 1 (Gerhards et al. 1966) and thus becomes orally active. It is free of liver toxicity. Unlike testosterone mesterolone cannot be metabolized to estrogens (Breuer and Gütgemann 1966) and acts, like DHT, on a molecular level. It has only limited effects in suppressing pituitary gonadotrophin secretion (Aakvaag and Stomme 1974; Gordon et al. 1975). It can only be considered a weak or partially active androgen. Altogether, mesterolone is not suited for the substitution of hypogonadism.

10.3.1.5 Testosterone undecanoate

When testosterone is esterified in the 17β-position with a long aliphatic side chain such as undecanoic acid and given orally, its route of absorption from the gastrointestinal tract is shifted from the vena portae to the lymph and reaches the circulation via the ductus thoracicus (Coert et al. 1975; Horst et al. 1976). Absorption is improved if the ester is taken in arachis oil (Nieschlag et al. 1975) and with a meal (Frey et al. 1979). After oral ingestion of a 40 mg capsule, of which 63% i.e. 25 mg is testosterone, maximum serum levels are reached 2 to 6 hours later (Nieschlag et al. 1975; Schürmeyer et al. 1983). Thus, with 2 to 4 capsules (80 to 160 mg) per day substitution of hypogonadism can be achieved. (For further pharmacokinetic considerations see Chapter 11 by Behre and Nieschlag in this volume).

Along with injectable testosterone esters, oral testosterone undecanoate belongs to the standard repertoire for the treatment of hypogonadism, although the widely fluctuating serum levels and the relavtively short-lived serum testosterone peaks make this type of therapy less than ideal.

10.3.2 Sublingual application

17α-methyltestosterone was found to be more effective when applied sublingually than when ingested orally (Escamilla 1949). This type of substitution should, however, not be practised because of the liver toxicity of methyltestosterone summarized above.

The solubility of the hydrophobic testosterone molecule can be enhanced by incorporation into hydroxypropyl-β-cyclodextrins (Pitha et al. 1986) which are macro-ring structures consisting of cyclic oligosaccharides. When testosterone incorporated into such cyclodextrins is administered sublingually steep increases in serum testosterone occur lasting for one or two hours (Stuenkel et al. 1991). Hypogonadal men treated with three daily doses for 60 days showed improvement of their condition (Salehian et al. 1995; Wang et al. 1996b). This is an interesting new approach to testosterone substitution, but unless more constant serum levels can be achieved this therapy would require repeated daily applications and would have the same disadvantages as conventional oral testosterone undecanoate therapy.

10.3.3 Rectal application

In order to avoid the first-pass effect of the liver, testosterone can be applied rectally in suppositories (Hamburger 1958). Administration of a suppository containing 40 mg testosterone results in an immediate and steep rise of serum testosterone lasting for about four hours. Effective serum levels can be achieved by repeated applications (Nieschlag et al. 1976). This therapy, however, never gained much popularity probably because the patients find it unacceptable to use suppositories three times daily on a long-term routine basis.

10.3.4 Nasal application

The first-pass effect of the liver can also be avoided by applying testosterone to the nasal mucosa (Danner and Frick 1980). However, unreliable absorption patterns and short-lived serum peaks prevent this form of application from becoming a desirable option for long-term substitution therapy and it has never passed the experimental state.

10.3.5 Intramuscular application

10.3.5.1. Testosterone esters

The most widely-used testosterone substitution therapy is the intramuscular injection of testosterone esters. While free unesterified testosterone has a half-life of only ten minutes and would have to be injected very frequently, testosterone esters have a prolonged half-life. To a certain degree the length of the ester moiety side chain determines the duration of action. Pharmacokinetic details of the esters will be discussed in Chapter 11 by Behre and Nieschlag. In short, for substitution purposes *testosterone propionate* must be injected every two to three days while *testosterone enanthate* when given in doses of 200 to 250 mg allows spacing of the injections at about two-week intervals. Two other clinically available testosterone esters, *testosterone cypionate* and *testosterone cyclohexanecarboxylate* have very similar kinetic properties to enanthate so that they can be used in the same doses and intervals (Gooren 1987; Nieschlag et al. 1976; Schulte-Beerbühl and Nieschlag 1980; Snyder and Lawrence 1980; Schürmeyer and Nieschlag 1984; Sokol et al. 1982).

The disadvantage of all these esters is that they produce initially supraphysiological testosterone levels which may exceed normal levels severalfold and then slowly decline, so that before the next injection pathologically low levels may be reached. The patients recognize these ups and downs of testosterone levels in parallel variations of the general well-being, sexual activity and emotional stability. Despite these disadvantages testosterone enanthate and cypionate are still the standard therapy for male hypogonadism.

Because of these shortcomings of the available esters the World Health Organization (WHO) initiated a steroid synthesis programme (Crabbé et al. 1980) out of which a series of new testosterone esters was developed. When tested in small laboratory rodents a specific ester was identified that showed greatly prolonged activity, namely *testosterone-trans-4-n-butylcyclohexyl-carboxylate*, free name *testosterone buciclate*. This ester was then tested in castrated monkeys and found to raise testosterone serum levels of the animals

into the normal range for about four months when a single dose of 40 mg was injected. The same amount of testosterone given as testosterone enanthate produced supraphysiological serum testosterone levels for eight days which returned into the subnormal range by three weeks (Rajalakshmi and Ramakrishnan 1989; Weinbauer et al. 1986). In a further preclinical study in monkeys testosterone buciclate in combination with a GnRH antagonist proved very successful in achieving azoospermia (Weinbauer et al. 1989). In a phase-I clinical study with hypogonadal men single injections of 600 mg testosterone buciclate produced serum testosterone levels in the normal range for 12 weeks (Behre and Nieschlag 1992). In a first clinical trial for hormonal male contraception single injections of 1000 mg showed a similarly long duration of action and were well tolerated by normal volunteers (Behre et al. 1995). Supraphysiologic levels were not observed at any point. Therefore, testosterone buciclate has the longest duration of action of any injectable ester tested so far and appears to have a great potential for clinical use. Further studies are awaited with great interest.

In China *testosterone undecanoate* dissolved in teaseed oil was first used for intramuscular injections and satisfactory results for the substitution of hypogonadism were reported (Wang et al. 1991). When tested in monkeys a half-life considerably longer than that for testosterone enanthate was found (Partsch et al. 1995). Ensuing phase-I and phase-II trials confirmed these findings so that testosterone undecanoate injections of 1000 mg (in castor oil) may allow injection intervals of up to 8 weeks (see Chapter 11 by Behre and Nieschlag, this volume). Thus, next to testosterone buciclate, the undecanoate ester appears to be a promising injectable preparation currently undergoing clinical testing.

10.3.5.2 Testosterone microspheres

Drugs can be incorporated into biodegradable microspheres. Such drug-loaded microspheres when injected intramuscularly provide controlled release of the substance for several weeks or even months. As an example, microencapsulated GnRH agonists have become a valuable modality in the treatment of prostatic carcinoma. Testosterone has been incorporated into poly (DL-lactide-co-glycolide) microspheres. When first tested in castrated monkeys single injections resulted in an elevation of serum levels above the lower limit of normal for several months (Asch et al. 1986). When similar microsphere injections containing 315 mg of testosterone were given to eight hypogonadal men serum testosterone levels slowly increased to peak levels at about eight weeks and fell thereafter to reach pathological levels again by 11 weeks (Burris et al. 1988). In a later study the size-range and the testosterone loading of the microspheres were adjusted so that in hypogonadal men single intramuscular injections resulted in relatively constant serum levels within the normal range for about 70 days (Bhasin et al. 1992). These two clinical studies demonstrated that the microspheres can be adapted to the required needs and the results were encouraging. However, no further development has occurred since, probably due to problems with stability and reproducibility of the microspheres (Bhasin and Swerdloff 1996).

10.3.6 Subdermal implants

Shortly after the chemical synthesis of testosterone it was used clinically in the form of implants. For this purpose testosterone was compressed into short rods which were then implanted subcutaneously and lasted for several weeks or months. With the advent of other modalities they went out of general use. However, recent investigations found favourable pharmacokinetic profiles with these implants (Handelsman et al. 1990; Jockenhövel et al. 1996) so that there is renewed interest (Nieschlag 1996). In this volume, this kind of substitution is discussed in Chapter 12 by Handelsman.

The use of testis-shaped testosterone-loaded implants were described by Japanese investigators (Kaetsu et al. 1988). The implants were prepared from 10 g vinyl monomer and 6.4 g testosterone by radiation-induced polymerisation. These artificial testes were placed in the scrotum of orchidectomized patients and provided serum testosterone levels sufficient for substitution for over a year. The implants serve the double function of a cosmetic and an endocrine prothesis. An analysis of the kinetic profiles more detailed than provided in the publications would be desirable to further explore this modality. However, further publications could not be traced and it proved impossible to contact the authors.

10.3.7 Transdermal testosterone

The skin easily absorbs steroids and other drugs and transdermal drug delivery has become a widely used therapeutic modality. Transdermal substitution of estradiol is now one of the general methods for treating ovarian insufficiency. For this purpose, however, only micrograms of estradiol are required, whereas milligrams of testosterone are necessary for treatment of male hypogonadism. Such large amounts of androgens can only be administered through the skin of the trunk if large areas are covered with androgens. Moreover, the dosage is difficult to control and accidental person-to-person transfer may occur as shown by androgenization of the female partners of men using androgen-containing creams (Delanoe et al. 1984). This kind of androgen treatment using DHT-containing creams is presented in Chapter 15 of this book by Schaison and Conzinet.

Different areas of the skin, however, show different rates of steroid absorption – the scrotum has the highest rate, about 40-fold higher than the forearm (Feldmann and Maibach 1967). This difference in absorption rates has been exploited for the development of a transdermal therapeutic system (TTS) to deliver testosterone. 40 and 60 cm^2 large polymeric membranes loaded with 10 or 15 mg testosterone, when attached to the scrotal skin, deliver sufficient

amounts of the steroid to provide hypogonadal men with serum levels in the physiological range (Bals-Pratsch et al. 1986; Findlay et al. 1987; Korenmann et al. 1987). The membranes need to be renewed every day. When applied in the morning and worn until the next morning the resulting serum testosterone levels resemble the normal diurnal variations of serum testosterone in normal men without supraphysiological peaks (Bals-Pratsch et al. 1988). More pharmacokinetic details and clinical experience with transscrotal testosterone therapy are provided in Chapter 13 by Atkinson in this book.

While testosterone is readily absorbed by genital skin, transdermal systems for use on non-genital skin require enhancers to facilitate sufficient testosterone passage through the skin. Such systems have recently become available for clinical use and are described in detail in Chapter 14 by Meikle and in Chapter 13 by Atkinson in this volume. If one or two such systems are worn for 24 hours physiologic serum testosterone levels can be mimicked, as with transscrotal patches (Brocks et al. 1996; Meikle et al. 1996). However, skin reactions occur at a higher rate due to the alcoholic enhancer used and the occlusive nature of the systems (Jordan 1997).

Nevertheless, both transdermal modalities through either scrotal or non-genital skin provide the most physiologic serum testosterone levels in comparison with all other available preparations.

10.4 Use of testosterone in male hypogonadism

The prime indication for testosterone is substitution therapy of male hypogonadism. An overview of the syndromes is provided in Table 10.2. Hypogonadism may be caused by hypothalamic, pituitary, testicular or target organ lesions (for a detailed description the reader is referred to the textbook by Nieschlag and Behre 1997). The clinical symptoms of all syndromes and disease entities are predominantly due to a lack of testosterone or its action. The most frequent disorders requiring testosterone substitution are Klinefelter syndrome, Kallman syndrome, idiopathic hypogonadotropic hypogonadism (IHH), anorchia and pituitary insufficiency. Some disorders such as varicocele, orchitis, maldescended testes and Sertoli-cell-only syndrome may not, or only eventually require testosterone substitution. Although discrete endocrine alterations may be noted by laboratory tests in these patients, the endocrine capacity of the Leydig cells remains high enough to maintain serum testosterone in the lower physiological range. In order to achieve fertility in patients with hypothalamic (IHH) or pituitary insufficiency, treatment with gonadotropins (hCG/hMG) or pulsatile GnRH may be required temporarily (e.g. Kliesch et al. 1994). Once a pregnancy has been induced these patients will go back on testosterone substitution. Cases with hypogonadism of testicular origin in whom infertility cannot be treated require testosterone substitution continuously. In all these patients testosterone substitution is a lifelong therapy.

Table 10.2. Overview of disorders with male hypogonadism (from Nieschlag and Behre 1997)

Hypothalamic-pituitary origin (hypogonadotropic syndromes = secondary hypogonadism)
- Idiopathic hypogonadotrophic hypogonadism (IHH) including Kallman syndrome
- Prader-Labhart-Willi syndrome
- Laurence-Moon-Biedl syndrome
- Constitutional delay of puberty
- Pituitary insufficiency/adenomas
- Pasqualini syndrome
- Hyperprolactinemia
- Hemochromatosis

Testicular origin (hypergonadotropic syndromes = primary hypogonadism)
- Congenital anorchia
- Acquired anorchia
- Klinefelter syndrome
- XYY syndrome
- XX male
- Noonan syndrome
- Gonadal dysgenesis
- Leydig cell tumours
- Maldescended testes
- Varicocele
- Sertoli-cell-only syndrome
- General disease e.g. renal failure, liver cirrhosis, diabetes, myotonia dystrophica
- Male pseudohermaphroditismus due to enzyme defects in testosterone biosynthesis or LH-receptor defects

Target organ resistance to androgens
- Testicular feminization
- Reifenstein syndrome
- Perineoscrotal hypospadia with pseudovagina
- Infertility with androgen resistance
- Receptor positive androgen resistance
- Undervirilised fertile male syndrome

There is general agreement that patients with "classical" disorders of primary or secondary hypogonadism should receive testosterone substitution therapy. However, there is a relatively large group of patients in whom hypogonadism develops as a corollary of other acute or chronic diseases. Although these patients lack testosterone and show symptoms of hypogonadism, testosterone is usually not administered to them. Just why substitution is withheld is not quite clear. Probably in many physicians' minds testosterone is predominantly associated with sexual functions. However, the better the general effects of testosterone on well-being, mood, bones, muscles and red blood are understood, the more testosterone substitution will be considered. Similarly, male senescence may be associated with symptoms of hypogonadism and, again, there is no general consensus whether testosterone substitution should be provided or not. Because of the controversies and unresolved problems surrounding these areas, two chapters of this volume are devoted to these topics, Chapter 16 by Kaufman and Vermeulen, "Androgens in